




Available online at  
 ScienceDirect  
www.sciencedirect.com

Elsevier Masson France  
  
www.em-consulte.com



## CLINICAL RESEARCH

# A randomised trial of three counselling strategies for lifestyle changes in patients with hypercholesterolemia treated with ezetimibe on top of statin therapy (TWICE)

Essai randomisé de trois stratégies de conseils de modifications du mode de vie chez des patients hypercholestérolémiques traités par ezetimibe en association à une statine (TWICE)

Philippe Gabriel Steg<sup>a,\*</sup>, Jean-Claude Verdier<sup>b</sup>,  
François Carré<sup>c</sup>, Bernadette Darne<sup>d</sup>,  
Alain Ducardonnet<sup>e</sup>, Gérard Jullien<sup>e</sup>,  
Michel Farnier<sup>f</sup>, Philippe Giral<sup>g</sup>, Robert Haïat<sup>h</sup>,  
on behalf of the TWICE Investigators, France

<sup>a</sup> Inserm U-698, université Paris-VII—Denis-Diderot, hôpital Bichat-Claude-Bernard, AP—HP, 46, rue Henri-Huchard 75018 Paris, France

<sup>b</sup> Institut Cœur Effort Santé, 75013 Paris, France

<sup>c</sup> CHU de Rennes, 35009 Rennes, France

<sup>d</sup> Monitoring Force France, 78600 Maisons-Laffitte, France

<sup>e</sup> Collège national des cardiologues français, 75014 Paris, France

<sup>f</sup> Le Point Médical, 21000 Dijon, France

<sup>g</sup> Hôpital Pitié-Salpêtrière, AP—HP, 75013 Paris, France

<sup>h</sup> CHI Poissy-Saint-Germain, 78100 Saint-Germain en Laye, France

Received 21 September 2008; received in revised form 21 October 2008; accepted 22 October 2008

Available online 20 November 2008

## KEYWORDS

Ezetimibe;  
Primary hypercholesterolemia;

## Summary

**Aims.** — To compare the impact of three patient counselling strategies for lifestyle changes and to assess the safety and efficacy of ezetimibe on top of statin therapy in hypercholesterolemic high risk patients.

\* Corresponding author. Fax: +33 1 40 25 88 65.  
E-mail address: [gabriel.steg@bch.aphp.fr](mailto:gabriel.steg@bch.aphp.fr) (P.G. Steg).

Lifestyle  
intervention;  
Stages of change

**Methods.** — Open, cluster randomized 3-parallel group trial. Physicians were randomized between patient motivation on: diet or physical exercise or both. Counselling was adapted to the patient's baseline Prochaska stage of change. High cardiovascular risk patients, with LDL-C above or equal to 3 mmol/L despite statin therapy for at least 3 months, were enrolled. Ezetimibe (10 mg/day) and patient counselling were started at the same time. Target goal was defined as total cholesterol less than 5 mmol/L and LDL-C above 3 mmol/L.

**Results.** — Overall 428 physicians enrolled 1496 patients. At baseline, LDL-C was  $3.9 \pm 0.9$  mmol/L and total cholesterol was  $6.1 \pm 1.1$  mmol/L. LDL-C decreased by  $-30.4 \pm 19.3\%$  and 869 (62%) patients achieved target goal. No difference was shown between randomisation groups. However, improvements in diet consumption patterns were more easily obtained than improvement in physical activity stage of change in non-active patient at baseline.

**Conclusions.** — The marked short-term impact ( $-30\%$ ) on LDL-C, although similar between the three groups, slightly exceeds usual LDL-C reductions achieved by this dose of ezetimibe. Decreasing fat consumption seems easier than increasing physical activity. This study confirms the good efficacy, short-term tolerability and safety of ezetimibe on top of statins.

© 2008 Elsevier Masson SAS. All rights reserved.

## MOTS CLÉS

Ezetimibe ;  
Hypercholestérolémie  
primaire ;  
Mesures  
hygiéno-diététiques ;  
Modèle de  
Prochaska ;  
Étapes de  
changement

## Résumé

**Objectif.** — Comparer trois stratégies de conseils de modification du mode de vie et évaluer la tolérance et l'efficacité d'ezetimibe ajouté au traitement par statine chez des patients hypercholestérolémiques à haut risque.

**Méthodes.** — Essai randomisé par grappes, en trois groupes parallèles, en ouvert. Les médecins étaient randomisés entre : motiver le patient sur le régime, motiver sur l'activité physique ou motiver sur les deux. Les conseils étaient adaptés au stade de motivation (stade de Prochaska) du patient. Les patients sélectionnés étaient à haut risque cardiovasculaire, avec un LDL-C supérieur ou égale à 3 mmol/L malgré un traitement par statine supérieur ou égal à trois mois. Ezetimibe (10 mg/j) et conseils au patient étaient débutés simultanément. L'objectif était cholestérol total inférieur à 5 mmol/L et LDL-C inférieur à 3 mmol/L.

**Résultats.** — Au total 428 médecins ont sélectionnés 1496 patients (LDL-C :  $3,9 \pm 0,9$  mmol/L, cholestérol total :  $6,1 \pm 1,1$  mmol/L). Le LDL-C a diminué de  $-30,4 \pm 19,3\%$  et 869 (62%) patients ont atteint l'objectif thérapeutique. Il n'a pas été mis en évidence de différence entre les groupes de randomisation. Il a été plus facile d'améliorer la motivation sur les habitudes alimentaires que sur l'activité physique des patients non encore passés à l'action à l'inclusion.

**Conclusions.** — Bien que comparable entre les trois groupes, la diminution importante ( $-30\%$ ) du LDL-C est légèrement supérieure à celle habituellement rapportée à court terme avec cette dose d'ezetimibe. Diminuer la consommation de graisses semble plus facile qu'augmenter l'activité physique. Cette étude confirme la bonne efficacité et la tolérance à court terme d'ezetimibe en addition à un traitement par statine.

© 2008 Elsevier Masson SAS. All rights reserved.

## Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
CK	creatinine kinase
GEE	generalized estimating equations
HDL-C	high-density lipoprotein cholesterol
HMG-CoA	hydroxy-methyl-glutaryl-coenzyme A reductase
LDL-C	low-density lipoprotein cholesterol
REML	restricted maximum likelihood
TG	triglycerides
TWICE	ezetimibe together with any statin cholesterol enhancement
ULN	upper limit of normal

## Background

Diet and physical activity are the key to the treatment of dyslipidemia and prevention of cardiovascular disease, whether used alone or in combination with drug therapy [1,2]. Therapeutic lifestyle changes confer large and usually more than additive benefits in terms of risk reduction [2,3].

Much has been learned during the past two decades about successful modification of diet and lifestyle parameters, using behavioural science [4–7]. For example, the Prochaska and DiClementi [8] "stages of change" model postulates that both cessation of high-risk behaviours and the acquisition of healthy behaviours involve progres-

sion through five stages of change: pre-contemplation, contemplation, preparation, action and maintenance [9]. This transtheoretical model has been shown to generalize across a broad range of problem behaviours (including diet, exercise and weight control) [10–12]. The stage of change was conceived to help or guide planned change efforts. This study was designed to estimate the feasibility of the estimation of stage of change in ambulatory hypercholesterolemic patients and to compare three motivation strategies adapted to the patient baseline stage of change.

Adding ezetimibe to ongoing statin therapy leads to substantial additional reduction in LDL cholesterol levels [13]. Ezetimibe was found to be safe and well tolerated in clinical trials. Post marketing studies allow a better assessment of drug safety in clinical practice. This post-marketing trial therefore provided an opportunity to confirm the safety and efficacy of ezetimibe treatment in co-administration with a statin in routine clinical practice.

## Methods

### Patients

Patients with primary hypercholesterolemia and low-density lipoprotein (LDL-C) greater or equal to 3 mmol/L (115 mg/dL) currently treated with a statin for at least 3 months and between the ages of 18 and 80 were enrolled. Patients were at high cardiovascular risk: secondary prevention (established cardiovascular organ damage or disease) or in primary prevention with one or more cardiovascular risk factors (diabetes mellitus, sustained arterial hypertension, current smoker, man aged 45 or older, menopause or woman aged 55 or older, family history of premature sudden death or myocardial infarction) other than hypercholesterolemia [2]. A family history of premature event was defined as a sudden death or myocardial infarction in a first degree male relative man before 55 or first degree female relative before 65 [2]. Before starting intervention, it was checked that TG level was below 4.52 mmol/L (400 mg/dL), liver transaminases (ALT, AST) less or equal to 2-fold the ULN, CK less or equal to 2-fold ULN and creatinin clearance (Cockcroft formula) higher than 30 ml/min.

Key exclusion criteria included:

- use of other lipid-lowering agents within the last 3 months including HMG-CoA reductase inhibitors other than the current statin, fish oils, cholestyramin, niacin (> 200 mg/day) and fibrates;
- any modification in the statin treatment within the last 6 weeks;
- any contra-indication to statin or ezetimibe treatment;
- myocardial infarction, unstable angina, coronary artery bypass surgery, or angioplasty (coronary or peripheral artery) within the last 3 months;
- any immunosuppressant including cyclosporine;
- uncontrolled hypothyroidism;
- active liver disease including known infection by HBs or HBe virus or known HIV infection.

## Study design

This is an open, cluster-randomised, 3-parallel group trial comparing three counselling strategies on lifestyle changes.

Cluster randomisation was used, i.e. the physician was chosen as the unit of randomisation, in an attempt to limit treatment contamination. Physicians were randomised in a 1:1:1 ratio before systematic screening and recruitment between [14,15]:

- motivation on diet (Group 1);
- motivation on physical activity (Group 2);
- both (Group 3).

The trial was approved by the ethic committee and all subjects gave written informed consent before participating. The ClinicalTrials.gov identifier of the trial is NCT00328523.

## Intervention

### Evaluation of patient stage of change

In all patients, Prochaska stage of change and physical activity were estimated before the start of intervention and at the end of intervention, using a self-administered questionnaire. French translation of validated questionnaires were used. The five stages of change were defined for dietary fat reduction and for a Mediterranean nutrition pattern, with respect to two aspects of a Mediterranean diet: consumption of fish and vegetables. These stages of change reflect participants' readiness to reduce their dietary fat intake and to adopt a Mediterranean diet [6,7]. The five stages of change were defined for physical exercise using four questions [11,12].

### Patient counselling

Patients received a leaflet corresponding to their Prochaska stage of change. The leaflet summarizes counselling given to the patient according to the randomisation group of the physician (counselling based on diet, physical activity or both). The patient leaflets for the various types of Prochaska stage and type of counselling (diet, or physical activity or both) are available online at [www.cncardio.org/news00010d08.asp](http://www.cncardio.org/news00010d08.asp).

Counselling was based on the Second Joint Task Force of European and other Societies on Coronary Prevention [16]. A Mediterranean diet was recommended in this trial as well as the recommendation to reduce fat intake, in order to have a low cholesterol diet. Patients were instructed to eat two or more servings of fruit per day, vegetables once per day at least and to replace red meat by fish twice per week [7,17,18]. Patients were also instructed to reduce butter, cream and cheese consumption [2]. As far as physical activity was concerned, patients were professionally encouraged and supported to increase their physical activity safely to a level associated with the lowest risk of cardiovascular disease. Aerobic exercise (e.g. walking, swimming or bicycling) for 20 min. three times a week was recommended. Physicians emphasized the importance of physical activity in giving the patient a sense of well-being. For the elderly

or poorly conditioned or, people in the pre-contemplation, contemplation or preparation stages of change, any amount of physical activity was recommended such as strolling or gardening with emphasis on the possible benefit.

Physicians were not prevented from giving any other oral counselling on lifestyle changes that they thought might be useful for the patient.

## Ezetimibe therapy

Ezetimibe therapy was not part of randomisation and all patients received ezetimibe in addition to the statin they already received. The statin dose was kept unchanged.

## Flow of the study

Fig. 1 summarizes the study design. At the end of a run-in period of 1–2 weeks and after counseling have been given, all patients were instructed to take ezetimibe 10 mg once daily in the evening on top of the dose of statin they already received.

Lipid and safety parameters were assessed after 6 to 10 weeks of ezetimibe treatment, in a core laboratory [19]. At the third and last visit in the trial, performed one week after blood sampling, all patients were asked to complete the same self-administered questionnaire in order to estimate physical activity and the stages of change for physical exercise, dietary fat reduction and Mediterranean diet. Information on events and compliance with drug treatment were also recorded.

## Statistical analysis

The primary efficacy criterion was the percentage of patients with total plasma cholesterol (TC) less than 5 mmol/L (190 mg/dL) and LDL-C above 3 mmol/L (115 mg/dL) at the end of the trial, 6 to 10 weeks after the start of intervention [1]. The secondary efficacy criteria were:

- the percentage changes in LDL-C, HDL-C and TG from randomization to endpoint after 6–10 weeks of ezetimibe treatment;
- the percentage of patients with LDL-C less than 2.58 mmol/L (100 mg/dL) at the end of the trial;
- the percentage of patients with estimation of stage of change;
- the percentage of patients in a pre-action stage of change (precontemplation or contemplation or preparation stage of change) at baseline having moved to an action stage of change at end of trial.

Safety and tolerability of treatment were secondary criteria.

It was estimated that at most 70% of the patients would achieve target lipid level and that each physician would include three patients [20]. In a conventional randomised trial, without cluster design, 996 patients in every treatment group enabled detection of a difference between two treatment groups of 6% at least, with 80% power, at the 5% significance level [21]. For a cluster-randomised trial, using an intracluster correlation factor of 0.019, the standard sample estimates had to be inflated by a factor of 1.038

[14,22,23]. Therefore, a total of 3102 patients had to be enrolled by 1034 physicians.

The unit of analysis is the patient [14]. Categorical parameters were compared between the three therapeutic strategies using a chi-square adjusted for intracluster correlation, followed by logistic GEE using a model including terms for treatment, baseline LDL-C, age, gender, baseline stage of change and statistically significant interaction terms [14,24]. Percentage change data were expressed as mean or median percentage change (95% CI). Percentage change of LDL-C and other lipid parameters were compared between the three therapeutic strategies using a mixed model REML, with intervention arm and covariates as fixed effects and cluster as random effect [25,26]. Adjustment was done on baseline LDL-C, age, gender, and baseline stage of change. Interaction terms were tested. Intracluster correlation coefficients were estimated from the data. Percentage of patients in a pre-action stage at baseline having improved their stage of change by at least one level at the end of the trial was compared between randomisation groups. However, in order to avoid problems related to multiplicity only evolution of Prochaska stages of change for fat consumption and physical activity were statistically compared and descriptive statistics were used for other Prochaska stages of change: fish and vegetable consumptions. Statistical analysis was based on Intent to Treat, including all patients having received one dose of ezetimibe at least and with one determination of LDL-C before and after start of ezetimibe. All patients having received one dose of ezetimibe at least were included in the safety analysis.

Statistical analysis was conducted using SAS® software Version 8.2 (SAS Institute, Inc., Cary, NC).

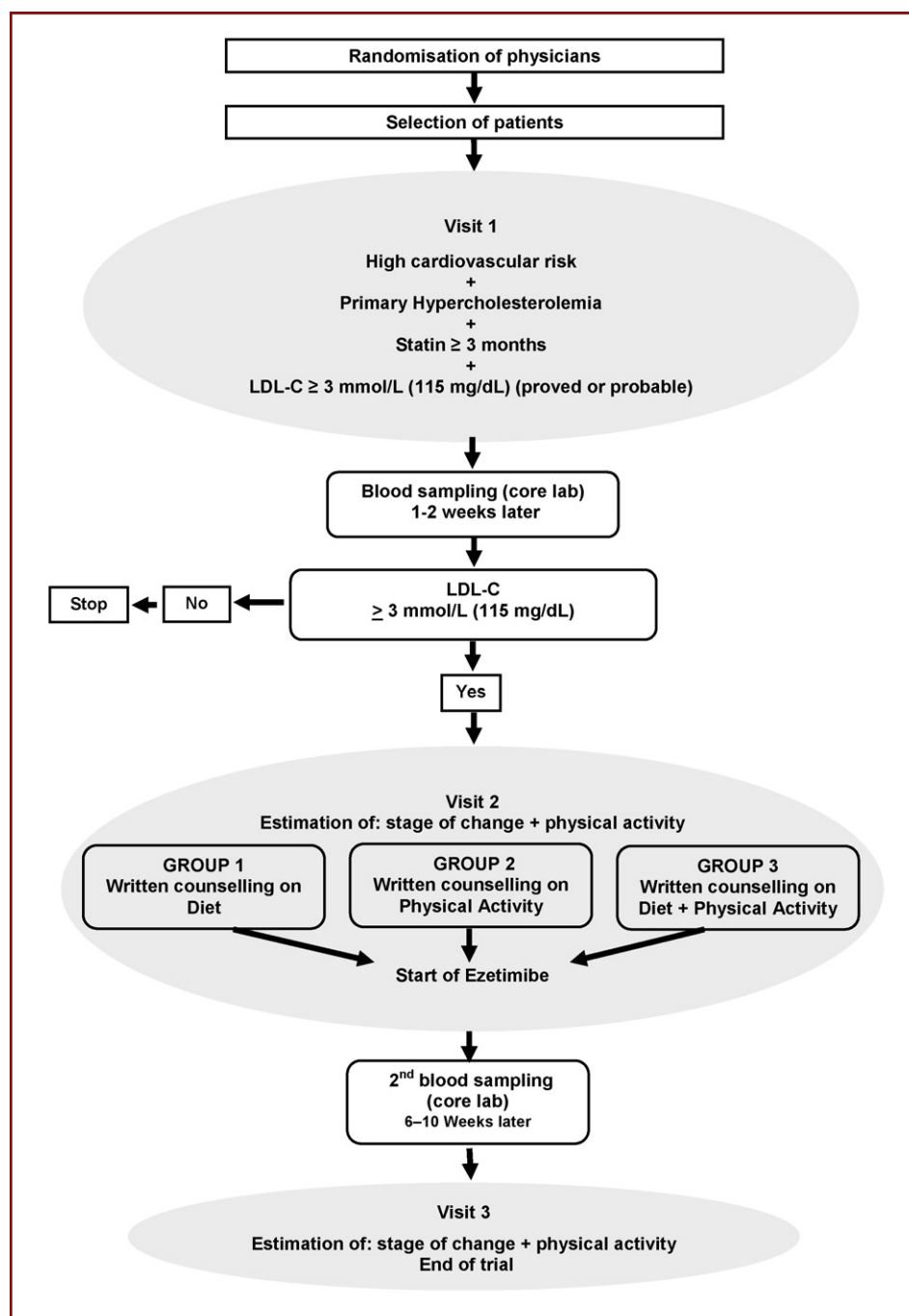
## Results

Out of 1059 randomised physicians (978 cardiologists and 81 general practitioners [GP]) 506 physicians (438 cardiologists and 68 GP) selected 2232 patients between June 2004 and December 2005. Enrollment, being much lower than anticipated, was stopped after 2232 patients were enrolled by 428 physicians. Of the 2232 patients, 1496 (67%) had received at least one dose of ezetimibe; 1411 (94%) patients were included in the efficacy analysis: 493 patients in Group 1, 490 patients in Group 2 and 428 patients in Group 3.

## Patient characteristics

Baseline demographics, medical history and lipid levels were similar between treatment groups (Table 1). Approximately one-third of the patients had a known history of myocardial infarction, and approximately half were treated for hypertension. At baseline, LDL-C was  $3.9 \pm 0.9$  mmol/L ( $151 \pm 35$  mg/dL) and total cholesterol was  $6.1 \pm 1.1$  mmol/L ( $234 \pm 39$  mg/dL).

Among statins used at baseline, pravastatin was the most commonly used ( $n=475$  [34%]), followed by atorvastatin ( $n=401$  [29%]), rosuvastatin ( $n=188$  [13%]), simvastatin ( $n=185$  [13%]), and fluvastatin ( $n=153$  [11%]). The median daily statin dose was 10 mg for rosuvastatin, 20 mg for



**Figure 1.** Design of TWICE. Physicians were randomised and trained before starting patients selection.

atorvastatin, pravastatin and simvastatin and 80 mg for fluvastatin.

In general, the three motivation groups were well balanced regarding Prochaska stages of change. At baseline, compliance with dietary guidelines was more frequent than compliance with physical activity guidelines: nearly 60% of the patient reported restriction in fat diet for more than 6 months when only approximately 45% of the patient reported exercising three times or more per week during at least 20 min. for more than 6 months.

After the initial blood sampling and before the start of intervention, irrespective of the motivation randomisation

group, most of the patients were motivated on diet and physical exercise. In fact, more than three quarters of the physicians gave oral counselling on lifestyle change not given by randomisation group in addition to the leaflet of their randomisation group (Table 2).

### Improvement in stage of change in patients in a pre-action stage at baseline

At the end of the trial, most of the patients in a pre-action stage of change at baseline had improved their Prochaska



**Table 1** Baseline characteristics of patients by motivation randomisation groups.

	Diet <i>n</i> = 493	Physical activity <i>n</i> = 490	Both <i>n</i> = 428
Age (years)	60.4 (10.6)	60.5 (11.1)	61.0 (10.7)
Male	325 (66)	330 (67)	267 (62)
BMI (kg/m <sup>2</sup> )	27.2 (4.2)	27.2 (4.3)	27.1 (4.0)
Obesity	105 (21)	115 (23)	91 (21)
Current smoker	72 (15)	61 (12)	58 (14)
Treated hypertension	258 (52)	228 (47)	227 (53)
Diabetes mellitus	57 (12)	57 (12)	38 (9)
Microalbuminuria	11 (2)	11 (2)	11 (3)
History of coronary artery disease	220 (45)	233 (48)	194 (45)
History of myocardial infarction	111 (34)	106 (31)	71 (24)
Lower limb arteriopathy	48 (15)	41 (12)	45 (15)
Total-C (mmol/L)	6.1 (1.1)	6.0 (1.1)	6.0 (0.9)
LDL-C (mmol/L)	3.9 (0.9)	3.9 (1.0)	3.9 (0.8)
HDL-C (mmol/L)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)
TG (mmol/L)	1.7 (0.9)	1.6 (0.9)	1.6 (0.8)
Mean (standard deviation) or No. patients (%).			

stage of change by at least one level whatever the lifestyle parameter (Fig. 2). Among the 593 patients who were in a pre-action stage of change for physical activity at baseline, 300 (50.6%) patients had improved their stage of change by at least one stage by the end of the trial and most of them had started to exercise at least three times per week for 20 min. This proportion was evenly distributed across physician randomization groups ( $p=0.21$ ).

On the other hand, 142/216 (65.7%) patients with no restriction in fat diet at baseline had improved their stage of change by at least one stage at end of trial (Fig. 2). Patients of Group 2 in a pre-action stage of change for fat consumption at baseline were less likely to have started decreasing fat consumption at end of trial than in the two other randomisation groups (Fig. 2,  $p<0.001$  between groups).

### Lipid data at end of trial

The mean duration of ezetimibe treatment was  $72 \pm 16$  days. Overall, 869 (62%) patients achieved target lipid goals (defined as LDL less than 3 mmol/L [115 mg/dL] and total cholesterol less than 5 mmol/L [190 mg/dL]) (95% confidence interval [59%–64%]). No significant difference was shown between groups ( $p=0.34$  with no adjustment except on cluster,  $p=0.50$  after adjustment on all covariates)

(Fig. 3). In 725 (51%) patients, LDL-C was below 2.58 mmol/L (100 mg/dL) at the end of trial.

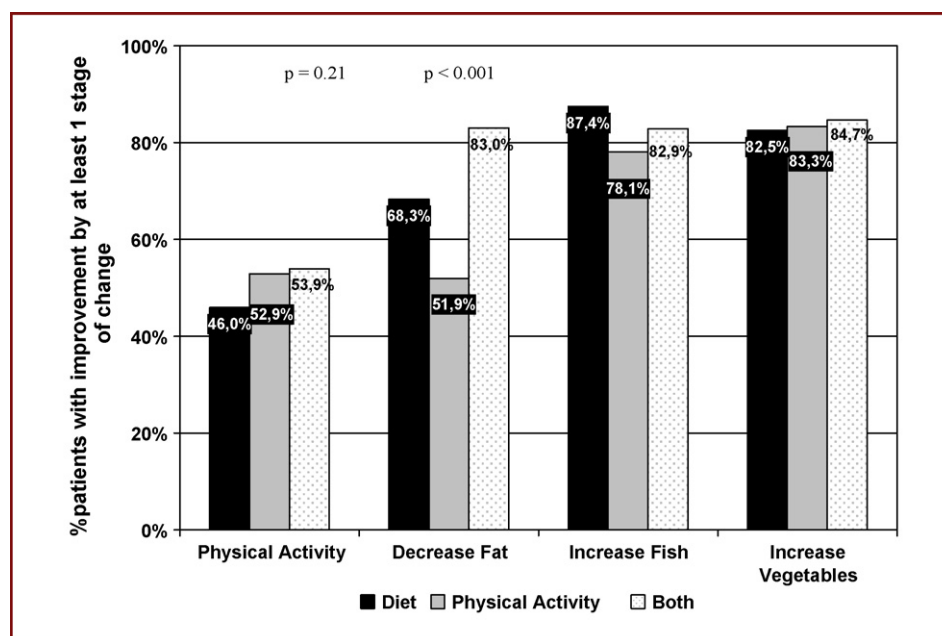
The mean effect on LDL-C lowering efficacy was  $30.4 \pm 19.3\%$  overall and was similar across randomization groups ( $p=0.82$  with no adjustment except on cluster,  $p=0.59$  between groups after adjustment on all covariates) (Fig. 4). No significant difference was found between randomisation groups for any of the lipid parameters (Fig. 4). Mean HDL-C did not change and TG slightly decreased ( $-7.5 \pm 35.6\%$ ) in all motivation randomisation groups ( $p=0.66$  between groups with no adjustment except on cluster,  $p=0.62$  after adjustment on all covariates).

### Safety and tolerability of ezetimibe

Elevations in CK  $\geq 5 \times$  ULN were observed in one patient at baseline and in two (0.1%) patients after start of ezetimibe. Transaminases  $\geq 3 \times$  ULN were observed in four (0.3%) patients at baseline and in one (0.1%) patient on statin and ezetimibe. No rhabdomyolysis (defined as reported by the investigator or CK  $\geq 5 \times$  ULN with clinical symptoms or CK  $\geq 10 \times$  ULN with or without clinical symptoms) was reported. Myalgia or cramps were recorded in 38 (3%) patients on statin and ezetimibe. Treatment was stopped because of side effects in 50 (3%) patients.

**Table 2** Motivation of the patient by the physician by physician randomisation groups.

Counselling given by the physician	Randomisation group of the physician		
	Diet <i>n</i> = 493	Physical activity <i>n</i> = 490	Both <i>n</i> = 428
Counselling on diet	481 (98%)	383 (78%) <sup>a</sup>	402 (94%)
Counselling on physical activity	359 (73%) <sup>a</sup>	476 (97%)	403 (94%)
<sup>a</sup> Oral counselling on lifestyle change not given by randomisation.			



**Figure 2.** Percentage of patients in a pre-action stage of change at baseline with at least one improvement in stage of change. Pre-action is defined by a precontemplation, contemplation or preparation stage of change. Only patients in a preaction stage of change at baseline are displayed. Preaction = precontemplation, contemplation or preparation stage of change. Statistical comparison between groups done only for Physical activity and Decrease in fat consumption.

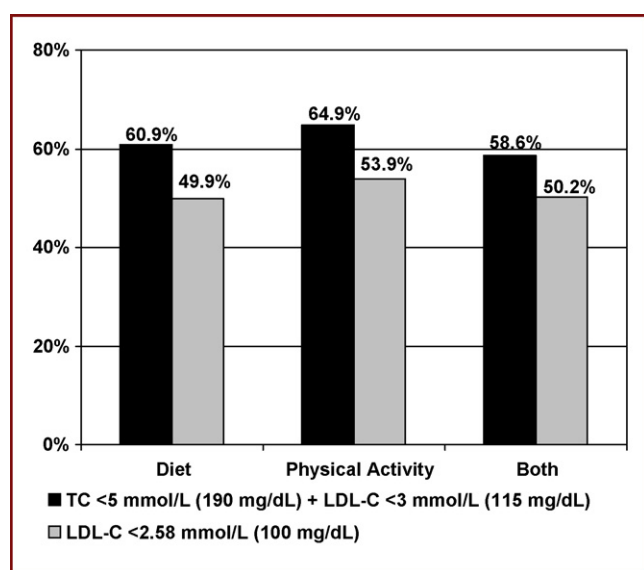
## Discussion

This trial is the first to compare patient counselling strategies in patients at risk of cardiovascular disease using the Prochaska transtheoretical model.

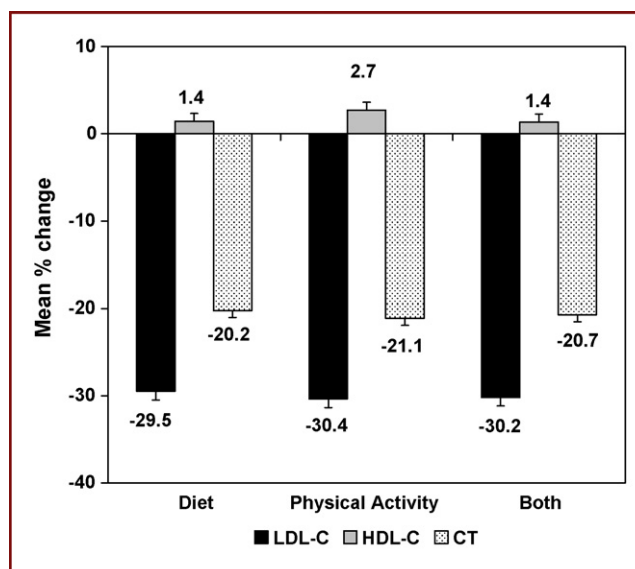
It seems easier to make a patient decrease his/her fat consumption than to start or increase physical exercise. In TWICE, compliance with diet guidelines was more often reported at baseline than compliance with physical exercise recommendations and with intervention, stage of change for fat consumption was more likely to improve than stage of

change of physical exercise in pre-action patients. This is at odds with a previous study performed in the United States which reported that physical activity was more improved than fat consumption [27]. Country habits might explain this discrepancy.

Within the TWICE study, ezetimibe and lifestyle changes were very effective in achieving LDL targets in high-risk patients with persistently elevated cholesterol levels despite statin monotherapy. LDL-C through the use of statins has been shown to be an extremely effective method for



**Figure 3.** Percentage of patients at cholesterol target goals after treatment by motivation randomisation groups.



**Figure 4.** Mean percentage change in lipid parameters by motivation randomisation groups. Mean percentage change with standard error (adjustment on cluster only).

lowering cardiovascular risk [28]. Within the TWICE study, if the administered statin dose was often lower than the standard statin dose, the 30% LDL-C reduction observed in the present study is more important than what might have been expected after doubling the statin dose and slightly more than the 25–26% expected after addition of ezetimibe in the context of clinical trials [13,29–31]. In another study in 256 patients, treated by statin for at least four weeks, addition of ezetimibe led to a more than 35% LDL-C reduction, however, statin doses were lower than in the present trial [32].

Although the interpretation is limited by intergroup crossover by physicians, a smaller than anticipated trial size and by the absence of a true control group managed conventionally without structured counselling, the almost identical lipid changes observed in the three groups suggest that all motivation strategies have similar and possibly limited short term efficacy on lipids. This is consistent with other published studies [33–35]. In TWICE, counselling was given only once and it cannot be ruled out that repetition of counselling over a longer duration would have impacted more lipid outcomes. Furthermore, long-term changes in lifestyle, including physical exercise and diets high in fruits, vegetables, whole grains, and unsaturated fatty acids are expected to decrease cardiovascular risk per se independently of their effect on conventional risk factors [2].

According to the European guidelines on cardiovascular prevention, moving forward in small consecutive steps is one key to successful long-term change in behaviour [36]. However, results of the present study suggest that counselling on diet and physical activity can be given simultaneously as recommended by the French recommendations on treatment of dyslipidemia updated in 2005 [37]. It is noteworthy that TWICE was started before the release of those recommendations and was based on the European and American guidelines [1,2,16].

We cannot rule out that compliance to lipid-lowering medications also increased with intervention. It is estimated that 60% of individuals prescribed lipid-lowering medications are non adherent and motivation based on the Prochaska transtheoretical model improves adherence [27,38].

In this high-risk population, controlling cholesterol levels is of particular importance and the dramatic LDL-C reduction allows 62% of patients not controlled by statin monotherapy to reach the therapeutic goal. In addition, 51% of the patients had a LDL-C below 2.58 mmol/L (100 mg/dL) at trial end, a level which has been suggested to be an appropriate target for most of the patients at high-cardiovascular risk, according to the updated American and European guidelines; the last ones being made available after the start of TWICE [36,39].

Despite a greater reduction in LDL-C, the percentage of patients at goal in the TWICE study is slightly lower than in an American community-based, double-blind randomized trial of ezetimibe added to statin therapy [13]. However, baseline LDL-C levels (3.2 mmol/L) were lower than in the present study.

The present study confirms the good efficacy on lipid levels and short-term tolerability of ezetimibe added to lifestyle changes and statins.

## Conclusions

In conclusion, in the three groups, more than 60% patients met target LDL-C levels. The marked impact (–30%) on LDL-C, although similar between the three groups, slightly exceeds usual LDL-C reductions achieved by this dose of ezetimibe. Decreasing fat consumption seems easier than increasing physical activity. TWICE study confirms the good efficacy on lipid levels and short-term tolerability ezetimibe on top of statins.

## Funding

Funding and sponsorship for the TWICE trial were provided by Laboratoires Merck Sharp & Dohme-Chibret, Paris France, on behalf of MSP Singapore Company, LLC.

## List of the Investigators who enrolled at least one patient

AARRAS Reda 06240 BEAUSOLEIL (Cardiologue), ABOU BADRA Bernard 31076 TOULOUSE Cedex 3 (Cardiologue), ADEGNON Kedi 09200 St GIRON (Cardiologue), AGBESSI KOSSI Apollinaire 59000 LILLE (Cardiologue), AIMOUCH Naceur 27000 EVREUX (Cardiologue), AKESBI Abdel 95602 EAUBONNE (Cardiologue), ALBESSARD Franck 14000 CAEN (Cardiologue), ALLAOUCHICHE Thierry 13300 Salon de Provence (Cardiologue), ALMAZOR Michel 44600 St NAZAIRE (Cardiologue), AMEUR HEDRICH Christiane 68100 MULHOUSE (Cardiologue), AMLAIKY Ahmed 68200 MULHOUSE (Cardiologue), AMMOR Mohammed 81000 ALBI (Cardiologue), AMORETTI Richard 95000 CERGY (Cardiologue), ANAYE Basam 59120 LOOS (Cardiologue), ANDRIEU Marc 12000 RODEZ (Cardiologue), ANGUENOT Thierry 25000 BESANCON (Cardiologue), ANTELIN Charles-Harry 17000 LA ROCHELLE (Cardiologue), ARNOU Robert 49000 ANGERS (MG), ASSULIN Teddy 95310 St Ouen L'Aumone (Cardiologue), ASSUNCAO Armindo 59220 DENAIN (MG), ATTALI Pierre 67000 STRASBOURG (Cardiologue), AUBERGE Jean-Maurice 13270 fos sur mer (Cardiologue), AUBERT Jean-Marc 06370 Mouans Sartoux (Cardiologue), AUBERT Pierre 83110 SANARY SUR MER (Cardiologue), AUBRY Jacques 13150 TARASCON (Cardiologue), AUDOUIN Philippe 75007 PARIS (Cardiologue), AUIAIS Frédérique 44240 LA CHAPELLE SUR ERDRE (MG), AURE Pascal 49000 ANGERS (MG), AVINEE Pierre 80094 AMIENS Cedex 3 (Cardiologue), AYRIVIE Pierre-Antoine 34500 BEZIERS (Cardiologue), BAHSOUN Roda 31077 TOULOUSE Cedex (Cardiologue), BAILLY Sylvain 91390 MORSANG SUR ORGE (Cardiologue), BALADIER COULEAUD Valérie 91490 MILLY LA FORET (Cardiologue), BALIGADOU So Orianarain 62140 HESDIN (Cardiologue), BARBEAU Pascal 33200 BORDEAUX (Cardiologue), BARBIN Patrick 53200 CHÂTEAU GONTIER (MG), BARRIERE Serge 64500 St Jean De Luz (Cardiologue), BARTHES François 25300 PONTARLIER (Cardiologue), BASLE Jérôme 17137 NIEUL SUR MER (MG), BATTLE Louis 37000 TOURS (Cardiologue), BATY Alain 53000 LAVAL (MG), BAZILE Brigitte 31290 Villefranche De Lauragais (Cardiologue), BEARD Thierry 65000 TARBES (Cardiologue), BEIGBEDER Jean-Yves 64000 PAU (Cardiologue), BELLEFLEUR



Jean-Paul 10120 St André- Les-Vergers (Cardiologie), BEMURAT Laurent 33610 CESTAS (Cardiologie), BENITAH Gérard 66100 PERPIGNAN (Cardiologie), BENITAH Elie 75010 PARIS (Cardiologie), BENOIT Pierre-Olivier 35033 RENNES Cedex 9 (Cardiologie), BERDAGUE Philippe 34500 BEZIERS (Cardiologie), BERDELLOU Thierry 93600 AULNAY S/ BOIS (Cardiologie), BERNARD Jean-Pierre 14000 CAEN (Cardiologie), BERNARD Jacques 59000 LILLE (MG), BERNARDEAU Claire 92150 SURESNES (Cardiologie), BERSAY Claude 75011 PARIS (Cardiologie), BERTHAUX Xavier 77220 TOURNAN EN BRIE (Cardiologie), BERTRAND Jean-Henri 84100 ORANGE (Cardiologie), BESSEKRI Abdelkader 67200 STRASBOURG (Cardiologie), BINEAU Bertrand 53950 LOUVERNE (MG), BINET Didier 50700 VALOGNES (Cardiologie), BLACHE Eric 13500 MARTIGUES (Cardiologie), BLANC Emile 20200 BASTIA (Cardiologie), BLANCHARD Benoit 76600 LE HAVRE (Cardiologie), BLISCAUX Pascale 57500 St AVOLD (Cardiologie), BODUR Gokhan 68100 MULHOUSE (Cardiologie), BOISSY Jean-Claude 83700 St RAPHAEL (Cardiologie), BOITTIN Philippe 14400 BAYEUX (Cardiologie), BOLTE Francois 82000 MONTAUBAN (Cardiologie), BONNAFFE Benoît 44600 St NAZAIRE (Cardiologie), BORFIGA Jean-François 85180 CHATEAU d'OLONNE (Cardiologie), BOUCHAYA Toni 82000 MONTAUBAN (Cardiologie), BOUCHET Gérard 84200 CARPENTRAS (Cardiologie), BOUCHUT Gilles 84800 L'Isle Sur La Sorgue (Cardiologie), BOUCLY Jean-Marc 59330 HAUTMONT (MG), BOUKHALIL Charles 72200 LA FLECHE (Cardiologie), BOURAS Yahya 90000 BELFORT (Cardiologie), BOURDON Catherine 13009 MARSEILLE (Cardiologie), BOURIAUD Michel 53950 LOUVERNE (MG), BOURNAZEL Vincent 49800 ANGERS (Cardiologie), BOUSQUET Jean-Pierre 13009 MARSEILLE (Cardiologie), BOUTAUD Philippe 86000 POITIERS (Cardiologie), BOUTON BROCHET Sophie 92250 La Garenne Colombes (Cardiologie), BOUVIER Eric 64300 ORTHEZ (Cardiologie), BRAL Michel 93000 STAINS (Cardiologie), BRAULT François 53200 CHATEAU GONTIER (MG), BREYSSE Hervé 13300 SALON De PROVENCE (Cardiologie), BROIN Patrick 74703 SALLANCHES (Cardiologie), BROUSSE Frédéric 74200 THONON Les BAINS (Cardiologie), BROTTIER Luc 64200 BIARRITZ (Cardiologie), BRUA Jean-Luc 57400 SARREBOURG (Cardiologie), BRUMELOT François 38000 GRENOBLE (Cardiologie), BRUNHAUT PETAUT Myriam 63100 CLERMONT-FERRAND (Cardiologie), BRUNET Eric 59590 RAISMES (MG), BUISSON Pierre 69001 LYON (Cardiologie), BURGGRAF Christian 25200 MONTBELIARD (Cardiologie), BUSSIÈRE Jean-Louis 74100 ANNEMASSE (Cardiologie), CADILHON Jean-Claude 33120 ARCACHON (Cardiologie), CAILLAT Muriel 92100 Boulogne Billancourt (Cardiologie), CAILLAUX Bruno Xavier 21000 DIJON (Cardiologie), CARETTE Bernard 51100 REIMS (Cardiologie), CASTER Luc 31400 TOULOUSE (Cardiologie), CAUDMONT Sébastien 59410 ANZIN (Cardiologie), CAUET Jacques 59100 ROUBAIX (Cardiologie), CAYOL Claude 13160 Châteaurenard (Cardiologie), CAZIER Yves 76100 ROUEN (Cardiologie), CESARINI Joël 91150 ETAMPES (Cardiologie), CHALTIEL Maurice-Gérard 38000 GRENOBLE (Cardiologie), CHANTRELLE Alain 31400 TOULOUSE (Cardiologie), CHARRAD Rafik 91160 LONGJUMEAU (Cardiologie), CHARRUAU Rémy 49800 TRELAZE (MG), CHEMIN Philippe 33200 BORDEAUX (Cardiologie), CHEVALIER Dominique 13010 MARSEILLE (Cardiologie), CHOPRA Soeb 78990 ELANCOURT (Cardiologie), CLARET-MONTE CATTINI Philippe 20220 L'ILE ROUSSE (Cardiologie), COHEN Alain 13002

MARSEILLE (Cardiologie), COIGNARD Elisabeth 93120 LA COURNEUVE (Cardiologie), COLIN Remy 83000 TOULON (Cardiologie), CONDOMINES Hervé 82000 MONTAUBAN (Cardiologie), CONDOURET Pierre 75009 PARIS (Cardiologie), CORBEL Claude 56110 GOURIN (Cardiologie), CORBIN André 22100 DINAN (Cardiologie), CORRAINI Bernard 03300 CUSSET (Cardiologie), COSSON Stephane 34500 BEZIERS (Cardiologie), COSTE LEENHARDT Corinne 13100 Aix En Provence (Cardiologie), COUDRAY Nicolas 06800 CAGNES SUR MER (Cardiologie), COUFFIN Jean-Pierre 78250 MEULAN (Cardiologie), COURDIER Guy 68100 MULHOUSE (Cardiologie), COURTAULT Alain 31700 CORNEBARRIEU (Cardiologie), CRESPY Richard 34000 MONTPELLIER (Cardiologie), DAFFOS Nicolas 93190 Sevran (Cardiologie), DAFFOS Catherine 93800 Epinay-Sur-Seine (Cardiologie), DAGRAN Olivier 13500 MARTIGUES (Cardiologie), DAHAN Simon Robert 67000 STRASBOURG (Cardiologie), DAHAN Jean-Maurice 06800 CAGNES SUR MER (Cardiologie), DAHAN Albert 31000 TOULOUSE (Cardiologie), DAILLET Etienne 84110 Vaison-la-Romaine (Cardiologie), DANÉY Dominique 33390 BLAYE (Cardiologie), DANY François 87000 LIMOGES (Cardiologie), DASSE Alain 53200 CHATEAU GONTIER (MG), DASSONVILLE Bernard 75014 PARIS (Cardiologie), DAVID Jean-Michel 53000 LAVAL (MG), DE ROQUEFEUIL Florence 75016 PARIS (Cardiologie), DEBOMY Alain 59000 LILLE (MG), DEHAUT Jean-Claude 02000 LAON (Cardiologie), DELBECQUE Danièle 59200 TOURCOING (MG), DELHOMME Claire 66000 PERPIGNAN (Cardiologie), DELOY Pierre-Philippe 84400 APT (Cardiologie), DELPLACE MAURY Christelle 37000 TOURS (Cardiologie), DELPONT Maurice 31240 ST JEAN (Cardiologie), DELUCHE Laurent 87100 LIMOGES (Cardiologie), DEMASLES Christian 65100 LOURDES (Cardiologie), DEMATTEO Philippe 50700 VALOGNES (Cardiologie), DENIS Lucien 42400 St CHAMOND (Cardiologie), DEQUEKER Jean-Luc 64100 BAYONNE (Cardiologie), DEQUIDT Bernard 76100 ROUEN (Cardiologie), DESRUES Hervé 53000 LAVAL (MG), DESTOMBES François 59940 ESTAIRES (Cardiologie), DESTRUBE Bernard 44240 LA CHAPELLE SUR ERDRE (MG), DEVOUASSOUX Charles 26400 CREST (Cardiologie), DIEBOLD Hervé 75116 PARIS (Cardiologie), DISY Jean-François 44600 St NAZAIRE (Cardiologie), DOMEREGO Jean-Jacques 06000 NICE (Cardiologie), DUC Philippe 94120 Fontenay Sous Bois (Cardiologie), DUCHENE Pierre 49460 FENEU (MG), DUCOS Cécile 33240 St André De Cubzac (Cardiologie), DUCOUDRE Michel 64200 BIARRITZ (Cardiologie), DUMORTIER Daniel 59800 LILLE (Cardiologie), DUPONT Thierry 59530 Le Quesnoy (Cardiologie), DURAFOURG Luc 11000 CARCASSONNE (Cardiologie), DURANDET Philippe 17000 LA ROCHELLE (Cardiologie), DUROY Christian 53000 LAVAL (MG), ELAHEE Abdoul 06150 Cannes La Bocca (Cardiologie), ELIAKIM Agnès 77270 VILLEPARISIS (Cardiologie), EOCHE Roger 44300 NANTES (MG), ESCARGUEL Didier 11000 CARCASSONNE (Cardiologie), ETLINGER Philippe 75009 PARIS (Cardiologie), EYMARD Claude 47000 AGEN Cedex (Cardiologie), FALK Claudine 92230 GENNEVILLIERS (Cardiologie), FALQUIER Jean-François 24100 BERGERAC (Cardiologie), FARAH Bruno 31076 TOULOUSE Cedex 3 (Cardiologie), FARGES Jean-Louis 62400 BETHUNE (Cardiologie), FAURE Olivier 11000 CARCASSONNE (Cardiologie), FAVREAU Bernard 49300 CHOLET (MG), FEDOROWSKY Alain 78800 HOUILLES (Cardiologie), FELDMANN Israel 67500 HAGUENEAU (Cardiologie), FERRER Jean-Claude 13150 TARASCON (Cardiologie), FERRINI Marc 69006

LYON (Cardiologie), FISCHBEIN Laurent 77500 CHELLES (Cardiologie), LINOIS Pascale 13340 ROGNAC (Cardiologie), FONTANEY Franck 42400 St CHAMOND (Cardiologie), FOUBERT Olivier 53200 CHÂTEAU GONTIER (MG), FOURNIER Jean-Bernard 30000 NIMES (Cardiologie), FOURNIER Jean-François 76190 YVETOT (Cardiologie), FOURNIER Eric 05000 GAP (Cardiologie), FRADIN Dominique 49300 CHOLET (Cardiologie), FRAYSSE Jean-Bernard 19100 Brive La Gaillarde (Cardiologie), FRITZ André 67600 SELESTAT (Cardiologie), FRUCHART Bruno 62400 BETHUNE (Cardiologie), GAILLARDE Bernard 66000 PERPIGNAN (Cardiologie), GALEY Arsène 02400 CHÂTEAU THIERRY (Cardiologie), GANDON Thierry 51100 REIMS (Cardiologie), GARANDEAU Marie 71600 Paray-Le-Monial (Cardiologie), GARCIA Philippe 83300 DRAGUIGNAN (Cardiologie), GARTENLAUB Olivier 94700 MAISONS ALFORT (Cardiologie), GASTON François Gilles 31320 Castanet Tolosan (Cardiologie), GAUSSERAND Michel 81000 ALBI (Cardiologie), GAUTHIER Jean 13200 ARLES (Cardiologie), GENOT Marcel 54000 NANCY (Cardiologie), GERBE Alain 14400 BAYEUX (Cardiologie), GERNIGON Patrick 44470 CARQUEFOU (MG), GILLET Thierry 83000 TOULON (Cardiologie), GIRAUD Patrick 84300 CAVAILLON (Cardiologie), GOBERT JACKEL Véronique 33150 CENON (Cardiologie), GOISSEN Patrick 40800 AIRE SUR ADOUR (Cardiologie), GOMBAUD Daniel 49000 ANGERS (MG), GORISSE Alain 59160 LOMME (MG), GOURDON Olivier 66000 PERPIGNAN (Cardiologie), GOURGON SARAZIN Dominique 78600 MAISONS LAFFITTE (Cardiologie), GRANGER Gérard 36100 ISSOUDUN (Cardiologie), GRAS Emmanuel 62110 HENIN BEAUMONT (Cardiologie), GRASSART Emmanuel 59138 BACHANT (MG), GRENIER Olivier Jean Yves 75008 PARIS (Cardiologie), GRIVET Bruno 69003 LYON (Cardiologie), GROS André 46000 CAHORS (Cardiologie), GUDIN DE VALERIN Michel 75116 PARIS (Cardiologie), GUEDJ Pierre 75009 PARIS (Cardiologie), GUEDJ Dominique 75116 PARIS (Cardiologie), GUERANGER Pierre 12200 Villefranche De Rouergue (Cardiologie), GUEZ Philippe 84200 CARPENTRAS (Cardiologie), GUILLEM Jean-Pierre 17000 LA ROCHELLE (Cardiologie), GUILLOT Philippe 34200 SETE (Cardiologie), GUILLOUX Jean-Paul 31410 LONGAGES (Cardiologie), GUIRCHOWSKI Alain 06300 NICE (Cardiologie), GURDA Marek 78500 SARTROUVILLE (Cardiologie), GUTEL Bertrand 95330 DOMONT (Cardiologie), HADDAD Jean-Claude PARIS (Cardiologie), HALFON Jean-Pierre 31270 CUGNAUX (Cardiologie), HALLALI Patrick 38000 GRENOBLE (Cardiologie), HALPHEN OVADIA Christine 78100 St Germain En Laye (Cardiologie), HAMEL Emmanuel 37000 TOURS (Cardiologie), HAMWI Abdel Hamid 75019 PARIS (Cardiologie), HANRION Pascal 49110 MONTREVAULT (MG), HASSAN Gilbert 13007 MARSEILLE (Cardiologie), HASSON Bernard 13009 MARSEILLE (Cardiologie), HELMS Eric 69800 St PRIEST (Cardiologie), HELOU Nabil 60300 SENLIS (Cardiologie), HERENT Marc 59410 ANZIN (MG), HETHUIN Jean-Michel 59400 CAMBRAI (Cardiologie), HEULS Sébastien 59650 Villeneuve D'Ascq (Cardiologie), HIJAZI Bernard 30900 NIMES (Cardiologie), HITA André 84400 APT (Cardiologie), HODROGE Henri 27200 VERNON (Cardiologie), HOFFMAN Olivier 75018 PARIS (Cardiologie), HOROVITZ Daniel 91600 Savigny Sur Orge (Cardiologie), HOURANY Antoine 14100 LISIEUX (Cardiologie), HUG Christian 66000 PERPIGNAN (Cardiologie), HUYGHE Dominique 59300 VALENCIENNES (MG), IGIGABEL Philippe 49125 TIERCE (MG), ISOARD Jacques 06140 VENCE (Cardiologie),

logue), JAUFFRET Bernard 13007 MARSEILLE (Cardiologie), JEAN Stéphane 17200 ROYAN (Cardiologie), JEANVOINE Henry 49000 ANGERS (Cardiologie), JELEN Pascal 17000 LA ROCHELLE (MG), JEREMIAZ Richard 75013 PARIS (Cardiologie), JOSEPH Jean-Paul 83150 BANDOL (Cardiologie), JUBERT Rémy 37300 JOUE LES TOURS (Cardiologie), JULIEN Bruno 40100 DAX (Cardiologie), JULLIEN Jean-Louis 75017 PARIS (Cardiologie), KADOUCHE James 75017 PARIS (Cardiologie), KALESKI Patricia 06600 ANTIBES (Cardiologie), KAYL BOILEVIN Dominique 57038 METZ Cedex 01 (Cardiologie), KEDRA Antoni Wojciech 75010 PARIS (Cardiologie), KERRAD Louisa 78450 VILLEPREUX (Cardiologie), KETELERS Régis 59280 ARMENTIERES (Cardiologie), KHAN Moin 02000 LAON (Cardiologie), KHAZNADAR Guy 75011 PARIS (Cardiologie), KHOURY François 11300 LIMOUX (Cardiologie), KHOURY Kamal 06190 Roquebrune Cap Martin (Cardiologie), KOHAN Patrick 54000 NANCY (Cardiologie), KORCZYNSKI Robert 26000 VALENCE (Cardiologie), KOZLOWSKI Francis 59200 TOURCOING (Cardiologie), KREBS Renaud 13200 ARLES (Cardiologie), KRONEK Didier 59590 RAISMES (MG), LABEDAN Frédéric 92500 RUEIL MALMAISON (Cardiologie), LABIB Marie 78340 Les Clayes Sous Bois (Cardiologie), LAGIEWKA Christian 93300 AUBERVILLIERS (Cardiologie), LAINE Eric 80094 AMIENS Cedex 3 (Cardiologie), LAISNE Raoul 53000 LAVAL (MG), LAMBERT Michel 49100 ANGERS (MG), LANDEL Rémi 22015 St BRIEUC Cedex 1 (Cardiologie), LANG Philippe 68200 MULHOUSE (Cardiologie), LAPEYRE Guy 81000 ALBI (Cardiologie), LARLET Jean-Marie 56600 LANESTER (Cardiologie), LAUGA Dominique 64300 ORTHEZ (Cardiologie), LAURENT Jean-Claude 18100 VIERZON (Cardiologie), LAURIER Bernard 78400 CHATOU (Cardiologie), LAURY Patrice 12000 RODEZ (Cardiologie), LAVABRE Guy 83140 Six Fours Les Plages (Cardiologie), LAVIGNE Guy 37000 TOURS (Cardiologie), LE MENAGER Hervé 44000 NANTES (Cardiologie), LE PODER Jean-François 56100 LORIENT (Cardiologie), LEANDRI Michel 63000 CLERMONT FERRAND (Cardiologie), LECERF Jean-Michel 59000 LILLE (Cardiologie), LEHUEUR Catherine 34110 FRONTIGNAN (Cardiologie), LEIBER Christian 68200 MULHOUSE (Cardiologie), LEJAY Dominique 59690 VIEUX CONDE (MG), LEMAIRE Pierre 62806 LIEVIN Cedex (Cardiologie), LENNE Philippe 06200 NICE (Cardiologie), LEPENNEC Pascale 49300 CHOLET (MG), LEROY Pierre 49000 ANGERS (MG), LEROY Yves 49000 ANGERS (MG), LERUSTE Sébastien 59310 LANDAS (MG), LEVEAU Xavier 49000 ANGERS (MG), LEVY Alain 75009 PARIS (Cardiologie), LEVY Richard 06700 St Laurent Du Var (Cardiologie), LEY Nicolas 65000 TARBES (Cardiologie), LIM Du Quang 92400 COURBEVOIE (Cardiologie), LOBEL Christian 62000 ARRAS (Cardiologie), LONGERE Philippe 83300 DRAGUIGNAN (Cardiologie), LONGUEVILLE Grégoire 58000 NEVERS (Cardiologie), LOPEZ Jean-Philippe 59330 HAUTMONT (MG), LORENTZ Christian 90000 BELFORT (Cardiologie), LOUCHARTE Jean-Christophe 62400 BETHUNE (Cardiologie), MACAREZ Marcel 59287 GUESNAIN (Cardiologie), MAES Damien 59200 TOURCOING (Cardiologie), MAFFERT Etienne 17000 LA ROCHELLE (Cardiologie), MAGNUS Patricia 68800 THANN (Cardiologie), MAICHE Elisabeth 44240 LA CHAPELLE SUR ERDRE (MG), MAIGNIEN Jean-Pierre 25000 BESANCON (Cardiologie), MAILLY Denys 31370 BERAT (Cardiologie), MAKKI Hamid 21400 Chatillon sur Seine (Cardiologie), MALDONADO Philippe 38130 ECHIROLLES (Cardiologie), MANCHET Guy 25000 BESANCON



(Cardiologue), MANLAY William 33000 BORDEAUX (Cardiologue), MANNESSIER Bruno 59243 QUAROUBLE (MG), MARACHLI Mathieu 18200 Saint Amand Montrond (Cardiologue), MARCO Frédéric 31400 TOULOUSE (Cardiologue), MARDEMOOTO Madhavan 30100 ALES (Cardiologue), MAREK Alain 80094 AMIENS Cedex 03 (Cardiologue), MARIN Denis 49125 BRIOLLAY (MG), MARLIER Mathieu 59130 LAMBERSART (MG), MARQUET Michel 05000 GAP (Cardiologue), MARTIN Michel 71600 PARAY LE MONIAL (Cardiologue), MARTIN Pierre-Etienne 13005 MARSEILLE (Cardiologue), MARTIN Olivier 06000 NICE (Cardiologue), MASSABIE Raymonde 78310 MAUREPAS (Cardiologue), MASSELOT Michel 62700 Bruay La Buissière (Cardiologue), MASSON Jean-Jacques 37700 St Pierre Des Corps (Cardiologue), MASSON Christophe 34080 MONTPELLIER (Cardiologue), MATHIEU Jean-Philippe 74000 ANNECY (Cardiologue), MAUDIERE Arnaud 37000 TOURS (Cardiologue), MAURICE William 49000 ANGERS (MG), MAURIN Philippe 48000 MENDE (Cardiologue), MAZE Jean Marie 49800 TRELAZE (MG), MEBARKIA Mansour 14400 BAYEUX (Cardiologue), MERCIER Gilles 59970 FRESNES SUR ESCAUT (MG), MEROUE Samuel 94110 ARCUEIL (Cardiologue), MESLI Zoubir 34070 MONTPELLIER (Cardiologue), MEYNIER Jean 87000 LIMOGES (Cardiologue), MICHEL Jean-Marie 67200 STRASBOURG (Cardiologue), MIKLER Francis 38600 FONTAINE (Cardiologue), MOJON Françoise 95330 DOMONT (Cardiologue), MOLINIER Françoise 31081 TOULOUSE (Cardiologue), MONIN Richard 26100 Romans Sur Isere (Cardiologue), MONKA Louis 06000 NICE (Cardiologue), MONNET DE LORBEAU Béatrice 41600 Lamotte Beuvron (Cardiologue), MONNIER Gilles 69250 Neuville Sur Saône (Cardiologue), MOREL Charles 42300 ROANNE (Cardiologue), MOTHES Philippe 64000 PAU (Cardiologue), MOUHAT Thierry 25400 AUDINCOURT (Cardiologue), MULLER Jean-Joseph 67000 STRASBOURG (Cardiologue), NAGENRANFT Bernard 95100 ARGENTEUIL (Cardiologue), NAVA Guy 26700 PIERRELATTE (Cardiologue), NECILI Yasmina 17000 LA ROCHELLE (Cardiologue), NEGRIER Michel 81400 CARMAUX (Cardiologue), OLIER Pierre 57150 Creutzwald (Cardiologue), OLIVIERI Bernard 06160 JUAN LES PINS (Cardiologue), OUAZANA Léon 75015 PARIS (Cardiologue), PALOMBA Alain 49000 ANGERS (MG), PAPOLA Philippe 57360 Amneville Les Thermes (Cardiologue), PAREATHUMBY Kumaressen 66500 PRADES (Cardiologue), PARRENS Eric 33200 BORDEAUX (Cardiologue), PASCARIELLO Jean-Claude 13008 MARSEILLE (Cardiologue), PASCO Alain 67800 Bischheim (Cardiologue), PECKRE Bernard 59910 BONDUES (MG), PEDEBOSCQ Georges 40000 MONT DE MARSAN (Cardiologue), PEDELHEZ Karine 59300 VALENCIENNES (Cardiologue), PELLISSIER Eric 06000 NICE (Cardiologue), PETIT Alain 62120 AIRE SUR LA LYS (Cardiologue), PETIT Luc 38000 GRENOBLE (Cardiologue), PEYRETOU Robert 33150 CENON (Cardiologue), PEYRONY Alain 79200 PARTHENAY (Cardiologue), PICARD Jean-Claude 07200 AUBENAS (Cardiologue), PICHON Eric 70000 VESOUL (Cardiologue), PIERI Bertrand 84120 PERTUIS (Cardiologue), PIERRON Fabrice 13380 Plan de Cuques (Cardiologue), PINZANI Alain 34200 SETE (Cardiologue), PLESKOF Alain 77500 CHELLES (Cardiologue), POLARD François 59000 LILLE (MG), POUCHOLON Elisabeth 31300 TOULOUSE (Cardiologue), POUJOIS Jean-Noël 08000 Charleville Mezieres (Cardiologue), PRADIES Félix 66500 PRADES (Cardiologue), PREISS Jean-Philippe 67000 STRASBOURG (Cardiologue), PRESTAT Marie-Paule 83400 HYERES (Cardiologue), PROST

Christophe 38200 VIENNE (Cardiologue), PROULT Marc 83110 SANARY SUR MER (Cardiologue), PRUNIER Laurent 93100 MONTREUIL (Cardiologue), PUEL Vincent 33000 BORDEAUX (Cardiologue), QUANDALLE Philippe 59100 ROUBAIX (Cardiologue), RAPHAEL Mikhael 13400 AUBAGNE (Cardiologue), RAYMOND Patrice 92600 Asnieres Sur Seine (Cardiologue), REGEARD Eric 63130 ROYAT (Cardiologue), REMAUD Philippe 49000 ANGERS (MG), RENAULT LAMAZE Guy 91540 MENECEY (Cardiologue), RENOUE Dominique 49300 CHOLET (MG), REYGROBELLET Pierre 34090 MONTPELLIER (Cardiologue), REYNERT Roland 67100 STRASBOURG (Cardiologue), RICHARD Philippe 09000 FOIX (Cardiologue), RICHARD GRACIET Joëlle 40000 MONT De MARSAN (Cardiologue), RIJAVEC Boja 25290 ORNANS (Cardiologue), ROBERT Patrick 53000 LAVAL (MG), ROBILLON Jean-Francois 98000 MONACO (Cardiologue), ROBIN Sébastien 17000 LA ROCHELLE (MG), ROBINE Jean-Philippe 69400 Villefranche Sur Saone (Cardiologue), RODIER Bernard 34000 MONTPELLIER (Cardiologue), ROLLAND Olivier 31080 TOULOUSE (Cardiologue), ROMANO Jean-Paul 13003 MARSEILLE (Cardiologue), ROOS Clément 67200 STRASBOURG (Cardiologue), ROSSET Michel 06200 NICE (Cardiologue), ROSSIGNOL Bruno 38028 GRENOBLE Cedex 1 (Cardiologue), ROUESNEL Philippe 41100 VENDOME (Cardiologue), ROUGE Jean-François 34120 PEZENAS (Cardiologue), ROUMANEIX Daniel 59220 DENAIN (MG), ROURE Brigitte 74400 Chamonix Mont Blanc (Cardiologue), ROVANI Xavier 77340 Pontault Combault (Cardiologue), RUAULT Pierre-Hervé 75016 PARIS (Cardiologue), SALAMA Angèle 28100 DREUX (Cardiologue), SALEH Bahige 69009 LYON (Cardiologue), SAMAMA Philippe 84200 CARPENTRAS (Cardiologue), SANANES Roland 77220 TOURNAN EN BRIE (Cardiologue), SANDALIAN Alain 13012 MARSEILLE (Cardiologue), SANDER Marc 78100 St Germain En Laye (Cardiologue), SARDA Robert 11000 CARCASSONNE (Cardiologue), SAVELLI Jacques 83700 St RAPHAEL (Cardiologue), SCHENOWITZ Alain 06000 NICE (Cardiologue), SCHOTT Bernard 67500 HAGUENAU (Cardiologue), SEBAOUN Edouard 13380 PLAN DE CUQUES (Cardiologue), SEBAOUN Alain 75015 PARIS (Cardiologue), SEKONIAN Richard 13012 MARSEILLE (Cardiologue), SENELLART François 38000 GRENOBLE (Cardiologue), SIBONY Yves 67600 SELESTAT (Cardiologue), SIGOGNEAU Jean-Marc 57400 SARREBOURG (Cardiologue), SIMONIN Annie 74100 ANNEMASSE (Cardiologue), SMADJA Danièle 59650 Villeneuve D'Ascq (Cardiologue), SOLANET Renaud 59100 ROUBAIX (MG), SOUKARIE Laurent 31650 St Orens de Gameville (Cardiologue), SPECHT Lionel 59130 LAMBERSART (MG), SPILLEMAECKER Benoît 85180 Château d'Olonne (Cardiologue), SPITERI Jean-Louis 75015 PARIS (Cardiologue), STIOUI Bernard 95140 GARGES (Cardiologue), SUSINI Georges 20200 BASTIA (Cardiologue), TABET Stéphane 95880 ENGHIEEN LES BAINS (Cardiologue), TARABBIA Philippe 64100 BAYONNE (Cardiologue), TARDIEU André 82000 MONTAUBAN (Cardiologue), TARDY Claude 66000 PERPIGNAN (Cardiologue), TESSIER Pascal 83700 St RAPHAEL (Cardiologue), THILLEUL Philippe 10000 TROYES (Cardiologue), THOIN Fabrice 13006 MARSEILLE (Cardiologue), THOMAS RICHARD Franck 18000 BOURGES (Cardiologue), TILMANT Pierre-Yves 59400 CAMBRAI (Cardiologue), TIMSIT Gilles 75019 PARIS (Cardiologue), TISON Eric 59800 LILLE (Cardiologue), TISSOT Marc 25300 PONTARLIER (Cardiologue), TOBAN Pascal 37100 TOURS (Cardiologue), TONDUT Jacques 49000 ANGERS (MG), TONDUT Jérôme 17000 LA ROCHELLE

(MG), TRAISNEL Gilles 59000 LILLE (Cardiologie), TRICOIRE Jacques 31000 TOULOUSE (Cardiologie), TRICOT Catherine 17000 LA ROCHELLE (Cardiologie), TRUONG MINH KY Bernard 64000 PAU (Cardiologie), TUBIANA Marie 06110 LE CANNET (Cardiologie), TURMEL Jacques 79000 NIORT (Cardiologie), URBINA Jean-Charles 59224 THIAIT (MG), VACOSSIN Christian 51200 EPERNAY (Cardiologie), VAISLIC Claude 78150 LE CHESNAY (Cardiologie), VALIN Marc 53001 LAVAL (MG), VASSEUR Philippe 62100 CALAIS (Cardiologie), VERSCHUEREN Philippe 77130 Montereau Fault Yonne (Cardiologie), VERVIN Pierrick 78600 MAISONS LAFFITTE (Cardiologie), VIAL Hubert 13008 MARSEILLE (Cardiologie), VIEL Christophe 17000 LA ROCHELLE (MG), VIGNE Jean-Marc 59600 MAUBEUGE (Cardiologie), VIOLET Thibaud 74000 ANNECY (Cardiologie), VIRCOULON Bernard 33220 Ste Foy La Grande (Cardiologie), VITOUX Jean-François 92000 NANTERRE (Cardiologie), VITTECOQ Bruno 91240 St Michel Sur Orge (Cardiologie), VOGEL Jacques 59170 CROIX (MG), VOGEL Marc 59390 TOUFFLERS (MG), VOGLIMACCI Michel 65000 TARBES (Cardiologie), WALCH Jean-Michel 93600 Aulnay-Sous-Bois (Cardiologie), WATTEAU Damien 44000 (Cardiologie), WAZANA Michel 67000 STRASBOURG (Cardiologie), WEILL Didier 88100 St DIE (Cardiologie), WIND Pierre 47200 MARMANDE (Cardiologie), WONG Olivier 84130 LE PONTET (Cardiologie), WORINGER Philippe 34800 Clermont l'Hérault (Cardiologie), ZARTARIAN Serge 06140 VENCE (Cardiologie), ZEITOUNI Roland 94250 GENTILLY (Cardiologie), ZITOUN Jacques 83200 TOULON (Cardiologie), ZYLBBERG Michel 12200 Villefranche De Rouergue (Cardiologie).

## References

- [1] Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice. *Eur J Cardiovasc Prev Rehabil* 2003;10:S1–10.
- [2] Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation* 2002;106:3121–43.
- [3] Kavanagh T. Exercise in the primary prevention of coronary artery disease. *Can J Cardiol* 2001;17:155–61.
- [4] Snetelaar LG. Nutrition intervention: lessons from clinical trials. In: Coulston AM, Rock CL, Monsen ER, editors. *Nutrition in the prevention and treatment of disease*. New York: Academic Press; 2001. p. 801 [Chapter 7].
- [5] Heins JM, Delahanty L. Tools and techniques to facilitate eating behaviour change. In: Coulston AM, Rock CL, Monsen ER, editors. *Nutrition in the prevention and treatment of disease*. New York: Academic Press; 2001. p. 801 [Chapter 8].
- [6] Curry JC, Kristal AR, Bowen DJ. An application of the stage model of behaviour change to dietary fat reduction. *Health Educ Res* 1992;7:97–105.
- [7] Siero FW, Broer J, Bemelmans WJE, Meyboom-de-Jong BM. Impact of group nutrition education and surplus value of Prochaska-based stage-matched information on health-related cognitions and on Mediterranean nutrition behavior. *Health Educ Res* 2000;15:635–47.
- [8] Prochaska JO, DiClemente CC. Stages and processes of self-change in smoking: toward an integrative model of change. *J Consult Clin Psychol* 1983;51:390–5.
- [9] Prochaska JO, DiClemente CC, Norcross JC. In search of how people change. Applications to addictive behaviours. *Am Psychol* 1992;47:1102–14.
- [10] Prochaska JO, Velicer WF, Rossi JS, et al. Stages of change and decisional balance for 12 problem behaviors. *Health Psychol* 1994;13:39–46.
- [11] Marcus BH, Rakowski W, Rossi JS. Assessing motivational readiness and decision-making analysis for exercise. *Health Psychol* 1992;11:257–61.
- [12] Marcus BH, Simkin LR. The stages of exercise behavior. *J Sports Med Phys Fitness* 1993;33:83–8.
- [13] Pearson TA, Denke MA, McBride PE, Battisti WP, Brady WE, Palmisano J. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEPATP III goals for LDL-cholesterol in hypercholesterolemic patients: the Ezetimibe Add-on to Statin Effectiveness (EASE) trial. *Mayo Clin Proc* 2005;80:587–95.
- [14] Donner A, Klar N. Design and analysis of cluster randomised trials in health research. London: Arnold; 2000.
- [15] Moore H, Summerbell CD, Vail A, Greenwood DC, Adamson AJ. The design features and practicalities of conducting a pragmatic cluster randomized trial of obesity management in primary care. *Stat Med* 2001;20:331–40.
- [16] Erhardt LR, Gotto A. The Evolution of European guidelines: changing the management of cholesterol levels. Review. *Atherosclerosis* 2006;185:12–20.
- [17] Keys A, Menotti A, Karvonen MJ, et al. The diet and 15-year death rate in the Seven Countries Study. *Am J Epidemiol* 1986;124:903–15.
- [18] Renaud S, deLorgeril M, Delaye J, et al. Cretan Mediterranean diet for prevention of coronary heart disease. *Am J Clin Nutr* 1995;61:1360S–7S.
- [19] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.
- [20] Gagné C, Bays HE, Weiss SR, et al., Ezetimibe Study Group. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 2002;90:1084–91.
- [21] Hintze J. NCSS, PASS and GESS. NCSS. Kaysville, Utah. [www.ncss.com](http://www.ncss.com) [consulté le 4 novembre 2008].
- [22] Parker DR, Evangelou E, Eaton CB. Intraclass correlation coefficients for cluster randomized trials in primary care: the cholesterol education and research trial (CEART). *Contemp Clin Trials* 2005;26:260–7.
- [23] Eldridge S, Cryer C, Feder G, Underwood M. Sample size calculations for intervention trials in primary care randomizing by primary care group: an empirical illustration from one proposed intervention trial. *Stat Med* 2001;20:367–76.
- [24] Heo M, Leon AC. Comparison of statistical methods for analysis of clustered binary observations. *Stat Med* 2005;24:911–23.
- [25] Singer JD. Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. *J Educ Behav Stat* 1998;24:323–55.
- [26] Evans BA, Feng Z, Peterson AV. A comparison of generalized linear mixed model procedures with estimating equations for variance and covariance parameter estimation in longitudinal studies and group randomized trials. *Stat Med* 2001;20:3353–73.
- [27] Johnson SS, Driskell MM, Johnson JL, et al. Transtheoretical model intervention for adherence to lipid-lowering drugs. *Dis Manag* 2006;9:102–14.
- [28] Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55000 vascular deaths. *Lancet* 2007;370:1829–39.

- [29] Foley KA, Simpson Jr RJ, Crouse III JR, Weiss TW, Markson LE, Alexander CM. Effectiveness of statin titration on low-density lipoprotein cholesterol goal attainment in patients at high risk of atherogenic events. *Am J Cardiol* 2003;92:79–81.
- [30] Gau GT, Wright RS. Pathophysiology, Diagnosis, and Management of Dyslipidemia. *Curr Probl Cardiol* 2006;31:445–86.
- [31] Armitage J. The safety of statins in clinical practice. *Lancet* 2007;370:1781–90.
- [32] González CA, Rubio-Guerra AF, Pavía A, Redding FJ, Cervantes JL, Zacarías JL, et al. Effectiveness and safety of ezetimibe added to statin therapy in patients with primary dyslipidaemia not achieving the LDL-C treatment goal on statin monotherapy. *Clin Drug Invest* 2007;27:333–7.
- [33] Clarke R, Frost C, Collins R, Appleby P, Peto R. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. *BMJ* 1997;314:112–7.
- [34] Vincent-Baudry S, Defoort C, Gerber M, Bernard MC, Verger P, Helal O, et al. The Medi-RIVAGE study: reduction of cardiovascular disease risk factor after a 3-mo intervention with a Mediterranean-type diet or a low-fat-diet. *Am J Clin Nutr* 2005;82:964–71.
- [35] Elley CR, Kerse N, Arroll B, Robinson E. Effectiveness of counselling patients on physical activity in general practice: cluster randomised controlled trial. *BMJ* 2003;326:793–8.
- [36] Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). European guidelines on cardiovascular disease prevention in clinical practice: executive summary. *Eur Heart J* 2007;28:2375–414.
- [37] Afssaps. Prise en charge thérapeutique du patient dyslipidémique. Mars 2005. 11 pages. Available at <http://agmed.sante.gouv.fr/pdf/5/rbp/dysreco.pdf>. Last Access 13 October 2008.
- [38] Luepker RV. Current status of cholesterol treatment in the community: the Minnesota Heart Survey. *Am J Med* 1997;102:37–42.
- [39] Grundy SM, Cleeman JI, Bariey Merz CN, et al. Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *J Am Coll Cardiol* 2004;44:720–32.